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UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

SANDOZ INC.,

Plaintiff,

v.

AMGEN INC.,

Defendant.

Case No. 2:22-cv-05326-RGK-MAR

DECLARATION OF ROBERT D. GIBBONS IN SUPPORT OF DEFENDANT AMGEN INC.'S MOTION IN LIMINE NO. 11 TO EXCLUDE CERTAIN OPINIONS OF DR. ROBERT MAKUCH

Complaint Filed: August 1, 2022
Pre-Trial Conference: July 24, 2023
Trial Date: August 8, 2023

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA
WESTERN DIVISION

SANDOZ INC., Plaintiff, vs. AMGEN INC., Defendant.	Case No. 2:22-cv-05326

Supplemental Declaration of

Robert D. Gibbons
Blum-Riese Professor of Biostatistics
University of Chicago

June 23, 2023

I, Robert D. Gibbons, declare:

1. I am the Blum-Riese Professor of Biostatistics and the Director, Center for Health Statistics, at the University of Chicago. I have been engaged by Amgen Inc. as an expert witness in this action.

2. I have reviewed the deposition of Sandoz expert Dr. Robert Makuch.[1] I have also reviewed the study protocol for the 2021 Sandoz Retrospective Study ("Sandoz Study") conducted by personnel at Sandoz Inc. ("Sandoz"), comparing incidence rates of febrile neutropenia (FN) in patients receiving pegfilgrastim via the prefilled syringe ("PFS") to those receiving pegfilgrastim via the on-body injector ("OBI").[2] (The Sandoz Study protocol is attached as Exhibit A.) Finally, I have reviewed an Excel spreadsheet of data ("data spreadsheet"), which appears to contain results of the Sandoz Study that informed the journal publication by personnel at Sandoz ("Sandoz Article").[3] (The Sandoz Article is attached as Exhibit B. The data spreadsheet is attached as Exhibit C.)

3. Based on my review of this evidence, it appears that the conclusion described in the Sandoz Article is the result of a selective presentation of study results by the personnel at Sandoz who conducted the study. In my experience as a member of the academic community and an elected member of the National Academy of Medicine, this would constitute scientific misconduct sufficient to justify a retraction of the Sandoz Article.

4. The Sandoz Article asserts the following as its conclusion: "In a matched cohort of patients representing real-world utilization, there was no statistically or

[1] Deposition of Dr. Robert Makuch, June 16, 2023, ("Makuch Deposition").
[2] SDZZIE-000259595–622.
[3] Ali McBride et al., "Economic and Clinical Outcomes of Pegfilgrastim via Prefilled Syringe vs On-Body Injector: A Real-World Data Analysis," *Journal of Managed Care and Specialty Pharmacy*, 27(9), September 2021, pp. 1230–1238; SDZZIE-000344544.xlsx.

clinically meaningful difference in FN incidence between OBI and PFS methods of pegfilgrastim administration."[4]

5. Sandoz used the Sandoz Article as an exhibit to its Complaint when it sued Amgen Inc. ("Amgen") in federal district court in California on August 1, 2022.[5] In the Complaint, Sandoz claims that certain Amgen promotional materials based on two Amgen studies (the "Amgen Studies") were false and misleading because, according to Sandoz, the Amgen Studies were not sufficiently reliable to support the promotional claims made.[6] Both Amgen Studies indicated a decreased incidence rate of FN in cancer patients undergoing myelosuppressive chemotherapy when the patients received pegfilgrastim via OBI versus PFS, likely because OBI improved compliance with timely delivery of the drug.

6. In the Complaint, Sandoz asserted that the Sandoz Article established the unreliability of the Amgen Studies, alleging as follows:

> "In fact, after seeing the abstract reflecting similar data to the 2019 Amgen Study and its obvious flaws, Sandoz employees and professional colleagues conducted an evaluation of the same patient population from the MarketScan databases reviewed in the abstract, and in a manner that was sufficient to withstand peer review. Unlike Amgen, Sandoz accounted for selection bias by using stringent inclusion and exclusion criteria to develop two patient cohorts with

[4] Sandoz Article, pp. 1230–1231.

[5] Complaint, *Sandoz Inc. v. Amgen Inc. and Amgen Manufacturing Limited*, August 1, 2022 ("Complaint"), ¶¶ 75, 118.

[6] The litigation brought by Sandoz challenges Amgen's promotional materials based on two Amgen studies: (a) a study estimating the rates of FN for Neulasta (pegfilgrastim) administered using a PFS versus the Onpro OBI in historical claims data ("2019 Amgen Retrospective Study") and (b) a study estimating the FN incidence rates by observing outcomes over a prospective prespecified study period in patients using OBI and comparing them to the outcomes observed in patients using other FN prophylaxis options ("2021 Amgen Prospective Study").

> comparable baseline characteristics in order that an appropriate comparison could be performed. In addition, Sandoz used an adequate power to detect differences in febrile neutropenia incidence between the treatment groups. Sandoz concluded that there was no statistically significant difference in febrile neutropenia incidence when administering pegfilgrastim prophylaxis via PFS or an on-body injector. The results of this study were subsequently published in a peer-reviewed journal. See Exhibit 3 (McBride, Ali et al., Economic and clinical outcomes of pegfilgrastim via prefilled syringe vs on-body injector: a real world data analysis, J Manag Care Spec Pharm, September 2021; 27(9):1230-38)."[7]

7. However, the deposition testimony of Dr. Makuch, the Sandoz Study protocol, and the data spreadsheet suggest that the Sandoz Study actually generated results very similar to the Amgen Studies. In fact, according to Sandoz's data spreadsheet, the results of Sandoz's pre-designated "main analysis" in the study protocol show that the magnitude of the reduction in the rate of FN associated with OBI, relative to that of PFS, is *larger* than that found in the Amgen Studies, and that this effect is *statistically significant*.[8] As such, it appears that the results of the "main analysis" of the Sandoz Study provide evidence in support of the conclusions of the Amgen Studies.

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[7] Complaint, ¶ 73.

[8] The data spreadsheet indicates that the adjusted all-cycles rates of FN were 2.91% (95% Confidence Interval ("CI") = (2.25%, 3.75%)) for the OBI group and 4.65% (CI = 3.67%, 5.87%) for the PFS group, corresponding to a statistically significant reduction in the rate of FN incidence associated with the use of OBI (p = 0.0096 and RR = 0.63). Further, the results of the unadjusted first-cycle analysis were also found to be statistically significant. The rates of FN were 3.13% (95% Confidence Interval ("CI") = (2.09%, 4.16%)) and 5.47% (CI = 4.49%, 6.46%), corresponding to a statistically significant reduction in the rate of FN incidence associated with the use of OBI (p = 0.0029 and RR = 0.57). SDZZIE-000344544.xlsx, tab "FN incidence"; SDZZIE-000259595–622 at 614.

8. The protocol for the Sandoz Study proposed three definitions of FN, where the "main analysis" would invoke the "main" definition of FN and the secondary analyses would invoke the "sensitive" and "specific" definitions of FN.[9] Sandoz conducted the "main analysis" pursuant to the protocol, but when reporting the results in the Sandoz Article, Sandoz reported only the results corresponding to the "sensitive" definition of FN.[10] The analysis using the "sensitive" definition of FN did not yield statistically significant results, although the OBI group did have a lower incidence rate of FN relative to the PFS group—a reduction that was similar in magnitude to that found in the Amgen Studies. However, the results for the "main analysis" (as presented in the data spreadsheet), which used the "main" definition of FN, showed statistically significant results in favor of OBI, even after the propensity score matching for confounding factors that Sandoz claimed was missing from the Amgen Studies as well as adjustment for correlated responses in the all-cycles analysis.[11] Despite this, authors of the Sandoz Article did not disclose that the analysis reported in the article differed from the "main analysis" specified in the study protocol. Assuming that the results in the data spreadsheet corresponding to the main endpoint are the actual results of the "main analysis," the Sandoz Article also failed to note that the definition of FN that Sandoz had designated as the "main" definition to be used in this "main analysis" yielded statistically significant results in favor of OBI.

9. I have also seen documents indicating that Sandoz was aware of these results in favor of OBI prior to submission of its article to JMCP. Before the

[9] SDZZIE-000259595–622 at 614.

[10] Sandoz Article, p. 1232 ("FN was defined as having a claim with a diagnosis code for neutropenia plus fever or infection on the same date, captured in each chemotherapy cycle from both medical inpatient and outpatient services, as previously validated."); SDZZIE-000259595–622 at 614 ("Sensitive Definition: Defined as diagnosis of neutropenia, with fever or infection (bacterial, fungal, or viral), in position one or two.").

[11] SDZZIE-000344544.xlsx, tab "FN incidence"; SDZZIE-000259595–622 at 614.

manuscript was finalized and submitted, the data spreadsheet noting the statistically significant results in favor of Onpro (highlighted by use of red text for the p-values of 0.0096, 0.0029, 0.0051 and 0.0022 for different analyses under the heading "for discussion") was forwarded along with the draft manuscript by one of the Sandoz Article authors to several Sandoz employees with the guidance "please don't share."[12]

10. JMCP's Author Guidelines note that submissions like the Sandoz Article should include "Results" that "report[] the ***primary*** findings, including the data points and statistical results" (emphasis added).[13] It appears that authors of the Sandoz Article failed to report the primary findings of its study. In the "Results" section of the Sandoz Article, Sandoz states:

> "3,152 patients were identified. After matching, the final sample included 2,170 patients, representing 1,085 in each cohort. The incidence of febrile neutropenia (FN) in the first chemotherapy cycle was 1.01% for OBI (95% CI = 0.56-1.82) vs 1.48% for PFS (95% CI = 0.91-2.39; P = 0.336). In all chemotherapy cycles (total cycles = 7,467), the FN incidence was 0.91% for OBI (95% CI = 0.64-1.30) vs 1.22% for PFS (95% CI = 0.90-1.64; P = 0.214). There was no statistically significant difference in adjusted per-member per-month all-cause total cost health care resource utilization (HCRU) for hospitalizations, emergency department visits, and pharmacy claims."[14]

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[12] SDZZIE-000344544, tab "FN incidence"; SDZZIE-000344523–4 at 3 (attached hereto as Exhibit D).

[13] JMCP Author Guidelines and Policies, *Journal of Managed Care and Specialty Pharmacy*, available at https://www.jmcp.org/authorguidelines, accessed on June 23, 2023.

[14] Sandoz Article, p. 1230.

Based on the underlying data spreadsheet, the statistics reported in the Sandoz Article are not the statistics for the "main analysis" using the "main" definition of FN, as outlined in the study protocol. The "main analysis" with statistically significant results in favor of Onpro is not mentioned in the article.

11. I understand that in its Complaint, Sandoz has further used the publication process and its securing of JMCP publication for the Sandoz Article to assert the importance of the fact that the 2019 Amgen Retrospective Study was never "the subject of a final manuscript published in a peer-reviewed journal and, therefore, has not been the subject of independent, rigorous scientific review."[15] Of course, peer review can only be rigorous if manuscript authors fully describe their study protocol and the results of their pre-specified analyses. If a protocol needs to be amended for some reason, there are procedures for doing so, with an explanation of the rationale. I have seen no evidence of a revision to the Sandoz Study's protocol. Selective submission of study results and withholding of primary findings would contravene established principles of scientific reporting.

12. I also note that when questioned about these issues in his deposition, Dr. Makuch failed to respond in ways that are consistent with professional scientific and statistical principles. Dr. Makuch surely knows that analysis of both the primary endpoint and all secondary endpoints that are pre-specified in the statistical analysis plan and study protocol are absolutely required in all submissions to the U.S. Food and Drug Administration, and that any selective reporting that favors a company's application is strictly prohibited. Nevertheless, it appears that Sandoz engaged in selective reporting in their publication. As described above, the Sandoz Article appears to report the analyses of only one of two secondary endpoints, neglects the results of the primary endpoint (which constitute statistically significant real-world evidence consistent with Amgen's study results finding that OBI is associated with a reduction in FN incidence rates

[15] Complaint, ¶ 107.

compared to PFS), and never mentions what the different prespecified study endpoints were.

13. Dr. Makuch appears to have been mistaken in deposition when stating that the Sandoz Article reported "the main definition, and…had two additional definitions:…a sensitive and specific."[16] In referring to the three definitions, he goes on to state "they proposed them I believe in the protocol, but they had a main definition that they used for their analysis."[17] With respect to the "main definition" Dr. Makuch stated "there was no ambiguity in that [Sandoz] prioritized … the main definition … for their analysis versus the other two definitions that they had."[18] When shown the Sandoz Article by opposing counsel in his deposition, Dr. Makuch continued to claim that it contained both the "main" analysis and the two sensitivity analyses as pre-specified in the Sandoz Study's protocol.[19] He claims to have checked whether what Sandoz was "indicating in the protocol was in fact reflected in what they had done" and concluded that "the answer was yes" and that "all three definitions are considered by Sandoz" in the Sandoz Article.[20]

14. When confronted with the fact that the Sandoz Article *only* reported the results of the secondary "sensitive" FN definition and asked in deposition if it would be appropriate to not report results of the analysis using the prespecified "main" FN endpoint, Dr. Makuch appeared to avoid the question. Dr. Makuch seems to excuse Sandoz's failure to report the results of the primary study endpoint by offering the justification that only "roughly one-third" of the p-values

[16] Makuch Deposition, p. 68:18–21.
[17] Makuch Deposition, p. 69:3–5.
[18] Makuch Deposition, p. 73:13–16.
[19] Makuch Deposition, p. 75:7–13 ("So I looked at the latter pages, pages 4 of 13, et cetera, to see that they did indeed use FN main, as I mentioned earlier without seeing the document, FN sensitive, and FN specific. So it certainly seemed to me that they were following what they had specified in the protocol.").
[20] Makuch Deposition, pp. 75:19–21, 149:1–2.

in the data spreadsheet are statistically significant.[21] Failure to report the results for the prespecified primary endpoint in a scientific publication is not acceptable scientific practice, and reporting the results of a secondary endpoint as though they were the results of the primary study endpoint is even more egregious. When questioned again about what the protocol had indicated as the "main analysis," Dr. Makuch then reversed his previous testimony and stated "I don't recall. I just recall…all three definitions being proposed, and to look at the protocol would show that."[22]

15. In summary, Sandoz defined a primary endpoint, which they referred to as the "main analysis" in their prespecified study protocol, and two secondary endpoints (one "sensitive" and one "specific") to be used as sensitivity analyses. Based on the data spreadsheet I have reviewed, it appears that in the Sandoz Article, Sandoz selectively reported results for the secondary "sensitive" FN endpoint, failing to even mention that there was a prespecified primary endpoint and that the results corresponding to that endpoint were statistically significant (consistent with the findings of the Amgen Studies). Such behavior would constitute scientific misconduct, and to the extent Dr. Makuch excuses this conduct, it is wholly improper. Provided that the results in the data spreadsheet corresponding to the main study endpoint are the results of the "main analysis" outlined in the study protocol, these statistically significant results confirm the results obtained in the two Amgen Studies regarding a statistically significant reduction in the FN incidence rate associated with the use of OBI relative to PFS.

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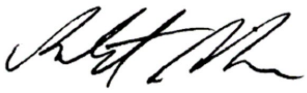
[21] Makuch Deposition, pp. 178:24–25, 179:1–9 ("I don't think -- you know, I don't know whether they were planning to do that or not, and I don't know what their internal process was for looking at things. I look at the data here, and I see two-thirds of the -- or more of the P values are not significant, and I see roughly -- roughly one-third of them being significant. So I see most of them being nonsignificant. And to decide on the definition of FN was clearly stated in the paper that they used.").

[22] Makuch Deposition, p. 179:16–18.

I declare under penalty of perjury that the foregoing is true and correct. Executed this 23rd day of June 2023 in Chicago, Illinois.



Robert D. Gibbons, Ph.D.